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Association between simple, combined lipid markers and 20-year cumulative incidence of type 2 diabetes: the ATTICA cohort study (2002–2022)

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Abstract

Background The aim of this study was to evaluate the association between simple, combined lipid biomarkers, and 20-year cumulative incidence of new type 2 diabetes mellitus (T2DM) among adults participating in the ATTICA cohort study (2002–2022).

Methods The present analysis included data from 2000 individuals free of T2DM at baseline (age 43 ± 13 years; 51% women). Sociodemographic, anthropometric, lifestyle, clinical, and biochemical parameters were collected at baseline and follow-up examinations; combined lipid markers were evaluated.

Results The 20-year cumulative incidence of T2DM was 26.3% (95%CI 24.4, 28.3%). All, simple and combined lipid markers were independently associated with new T2DM onset. The accuracy of simple and combined markers was approximately 75%, without any significant differences between simple and combined indices. The additive correct classification gain of lipid markers to glucose metabolism indices on 20-year new T2DM cumulative incidence varied between 0.9% for cardiometabolic index to 10.6% for LDL-cholesterol.

Conclusions Lipid profile is associated with the long-term onset of T2DM. Evaluated through simple or combined markers, lipid profiles can be utilized for identifying and improving risk stratification in individuals at high risk for T2DM, while also enhancing the effectiveness of primary prevention measures and public health strategies.

Keywords Lipid markers, Mediterranean diet, Incidence, Type 2 diabetes mellitus

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Background

Type 2 diabetes mellitus (T2DM) is a serious, chronic metabolic disorder that prevails at a large extent in the population worldwide [1]. According to the Institute for Health Metrics and Evaluation of the University of Washington, between 2022 and 2050, diabetes will have the third position, among the leading causes of disease burden, measured in number of disability-adjusted life years (DALYs), and among the non-communicable diseases [2]. In 2021, 966 billion USD were approximately expended concerning diabetes management, and the projection is considered to be 1,054 billion USD by 2045 globally, indicative of its catastrophic socioeconomic consequences [3].

Traditionally, lipid markers like total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs), have been used in cardiovascular risk assessment, but their role in predicting new T2DM onset seems also important. Insulin resistance has been associated with atherogenic dyslipidemia, i.e., increased level of triglycerides, decreased level of HDL-C, and changes in the composition of LDL-C (small and dense particles). In observational studies, T2DM has been strongly associated with increased levels of TGs, TC and LDL-C, as well as with decreased levels of HDL-C [4]. Accumulating evidence suggest that abnormal lipid levels are now considered as an independent risk factor for T2DM onset [5]. Furthermore, there is an increasing scientific interest for the study of combined lipid markers like, TC/HDL-C, LDL-C/HDL-C, and TGs/HDL-C ratios, or the Lipid Accumulation Product (LAP) that combines waist circumference (WC) and fasting TGs. Combined markers better reflect underlying metabolic dysfunctions, such as insulin resistance, which are closely related to new T2DM onset. Several studies have demonstrated the usefulness of the combined lipid markers in better predicting future T2DM cases in comparison with simple lipid markers [6–8].

In addition, overweight and obesity are recognized as a major predisposing factor of T2DM onset, with an alarming increasing economic burden [9, 10]. Excess body weight and T2DM demonstrate common pathophysiological mechanisms, and are considered major factors that contribute to the amplification of insulin resistance, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease [9–11]. However, the implication of body weight on the relationship between lipid markers and T2DM onset is not well understood [12].

Thus, the aim of the present study was to evaluate the association of both simple and combined lipid markers, and the cumulative incidence of T2DM, as well as the implication of body weight, among apparently healthy adults participating in the ATTICA cohort study (2002–2022) [13]. A conceptual hypothesis of the present study is that increased lipid markers' concentrations among apparently healthy adults (i.e., no history of cardiovascular disease or diabetes) are associated with excess cumulative incidence of T2DM within a long-time frame (i.e., 20-year), and this influence is moderated by body weight status levels.

Methods

Study design

The ATTICA study is a cohort study which was conducted during 2001–2002, in the Attica region [that covers 3.8 million population, living in urban (78%), and rural (22%), i.e., population density of less than 300 inhabitants per km^2 according to EuroStat areas], where Athens is the capital city of Greece. Three follow-up examinations were performed, i.e., at 2006 (5-year follow-up), 2012 (10-year follow-up) and 2022 (20-year follow-up). The main purpose of the ATTICA study was to evaluate the distribution of several sociodemographic, anthropometric, lifestyle, clinical, biochemical, and psychological parameters at 4 time points (including baseline), and their association with the long-term cardiometabolic disease incidence, including T2DM, in combination with the assessment of the trajectories of the above characteristics, along with their predictive significance. Information regarding the ATTICA study in terms of aims, design, sampling procedure as well as methodology may be found elsewhere in the literature [13].

Bioethics

The ATTICA study was conducted in consistent with the ethical guidelines laid down in the Declaration of Helsinki [14]. All procedures have been approved by the Ethics Committee of the First Cardiology Department of the National and Kapodistrian University of Athens (#017/01.05.2001), along with the Ethics Committee of the Harokopio University (#38/29.03.2022).

Sample

The exclusion criteria, regarding the participation in the ATTICA study, were the history of cardiovascular atherosclerotic disease, chronic viral infections, as well as living in institutions. The percentage of men and women who were excluded from ATTICA study, was 5% and 3%, respectively. A total of 4056 individuals who were invited to participate in the study, were randomly stratified by age, sex and region. Finally, 3042 subjects were recruited, i.e., participation rate 75%, after providing signed written consent, and were followed-up for 20 years; 1514 were men (aged 43±13 years; 18–87 years) and 1528 were women (aged 43±13 years; 18–89 years). A standardized protocol was used to evaluate the participants, either at their workplaces or their homes, by health professionals,

including cardiologists, nurses, general practitioners, and dietitians.

Measurements and clinical assessment

Baseline sociodemographic, anthropometric, lifestyle, clinical, and biochemicals parameters were evaluated through a detailed questionnaire and physical examination by the physicians of the study.

The measurement of anthropometric parameters, i.e., body weight (in kilograms), height (in m), as well as waist (in cm) and hip (in cm) circumferences, were carried out following a standardized protocol. Body mass index (BMI) was calculated as weight/height² (in kg/m²); overweight was defined as BMI between 25 and 29.9 kg/m² and obesity as BMI equal or above 30 kg/m² [15].

Blood samples at baseline examination were collected between 8 and 10 a.m., with participants in a sitting position as well as having fasted and avoided alcohol for 12 h. Various biochemical markers, namely TC, LDL-C, HDL-C, TGs, fasting glucose and fasting insulin were measured using appropriate laboratory methods. Serum TC, HDL-C, TGs, and glucose concentrations were measured using chromatographic enzymic method in a Technicon automatic analyzer RA-1000. LDL-C was calculated using the Friedewald formulae. Fasting insulin was measured by means of radioimmunoassay.

A variety of combined lipid markers were then calculated using the following formulas: Cardiometabolic index (CMI) by dividing TGs with HDL-C and multiplying by waist circumference to height ratio [16, 17], non-HDL to HDL Cholesterol Ratio (NHHR) by dividing non-HDL-C with HDL-C [18], and the triglyceride-glucose index (TyG) using the formula: ln(TGs*fasting glucose)/2 [19]. Lipid Accumulation Product (LAP) was calculated as $(WC_{cm} - 65) \times TG_{mmol/L}$ for males and $(WC_{cm} - 58) \times TG_{mmol/L}$ for females [16].

Clinical ascertainment

T2DM was defined as fasting glucose ≥ 125 mg/dL, or/and the use of antidiabetic medications; prediabetes was defined as fasting glucose between 100 and 125 mg/dL [20]. Arterial blood pressure was measured 3 times, and was averaged, with participants in a sitting position, after a 30-minute rest. Hypertension was defined as an average systolic blood pressure ≥ 140 mmHg and/or an average diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive drugs [21]. Hypercholesterolemia was defined as total cholesterol ≥ 200 mg/dL and/or the use of lipid-lowering agents [22].

Lifestyle assessment

Dietary assessment was conducted via a validated semi-quantitative food-frequency questionnaire, and habitual food intake was expressed as serving per day or week [23]. MedDietScore, an a priori diet index of 11 food components, with range between 0 and 55 points, was used to assess the adherence to the Mediterranean diet (MedDiet) [24]; higher values are indicative of higher adherence to the Mediterranean type of diet. The threshold used of the MedDietScore index was the median value 27, i.e., MedDietScore below 27 was indicative of low adherence, whereas above 27 entailed high adherence, respectively. Furthermore, MedDiet trajectories were identified to evaluate the level of longitudinal adherence to the MedDiet, during the 10-year follow-up, i.e., from baseline to 2012. Thus, four MedDiet trajectories were defined; increasing adherence level from low adherence at baseline examination to high adherence at 10-year follow-up, decreasing adherence level from high adherence at baseline to low adherence at follow-up, sustained high adherence (high adherence at both time points) and sustained low adherence (low adherence at both time points). The International Physical Activity Questionnaire (IPAQ), which was validated for the Greek population, was used to evaluate the level of physical activity of participants, concerning frequency (times per week), duration (in minutes per time), and intensity (expressed as calories per time) in a weekly base [25]. "Current smoking" was referred to the participants who had smoked ≥ 1 cigarette/day or had stopped smoking within the previous 12 months.

Follow-up examination

In 2022, information from 2169 out of 3042 individuals was available in the 20-year follow-up (participation rate 71%); 771 of the baseline participants were lost due to incorrect, missing, and changed addresses or telephone numbers, and 102 refused to participate in the 20-year follow-up examination. In case of death during the 20-year follow-up period, information was obtained either from relatives or medical records.

The endpoint of the present study was the onset of T2DM, defined according to the American Diabetes Association's criteria [20]. A total of 2138 adults (aged 44 ± 14 years; 18–89 years; 49% men) had complete information for the evaluation of the 20-year new T2DM cumulative incidence. However, 138 participants who had T2DM at baseline were excluded from the present analysis. Therefore, information concerning 2000 participants, 974 men (age 43 ± 13 years; 18–89 years) and 1026 women (age 42 ± 13 years; 18–89 years), was analyzed here.

Statistical analysis

Categorical variables are presented as relative frequencies (%) and continuous variables are presented as mean values [standard deviation (SD)]. The Pearson chi-square test was used to evaluate the association between

categorical characteristics. Associations between normally distributed variables and the new T2DM cumulative incidence were evaluated through the independent samples t-test, while their association with the trajectories of participants' adherence level to the Mediterranean diet was examined with the one-way Analysis of Variance (ANOVA). Whether these variables were normally distributed was tested through P-P plot and equality of variances through Levene's test. Bonferroni correction was applied in case of multiple comparisons. The main endpoint of the study was the 20-year cumulative incidence of new T2DM, and it was calculated as the ratio of new cases to the total number of participants in the 20-year follow-up. Odds Ratios (OR), as proxy of Relative Risks (RR), and corresponding 95% Confidence Intervals (95%CI) for the association of lipid markers with the examined endpoint within the 20-year follow-up period were evaluated through multivariable logistic regression analysis. Multi-adjusted logistic regression models were estimated for each simple or combined lipid marker, adjusted for several adjusting variables, i.e., age, sex, smoking status, physical activity level at baseline, fasting glucose, waist to hip ratio, use of lipid lowering medication or dietary supplements (plant sterols and stanols, fish oils, etc.), and family history of T2DM. Logistic regression analysis was applied, instead of survival models, because the exact time of onset of T2DM was not available in all cases at follow-up examination. C-statistic was calculated to evaluate the performance of the estimated risk models. Values > 0.70 indicate acceptable discrimination. The net reclassification index (NRI) was also calculated to quantify the improvement of models containing basic information versus the addition of lipid markers. STATA software, version 17 (MP & Associates, Sparta, Greece) was used for all statistical analyses. Two-sided level of significance was set at $p < 0.05$.

Results

20-year cumulative incidence of new type 2 diabetes

In total, 526 new cases of T2DM were observed during the 2002–2022 period, i.e., cumulative incidence rate of 26.3%. As it is presented in Tables 1 and 20-year cumulative incidence of new T2DM was significantly associated with older age, male sex, and increased anthropometric indices, and with worse glycemic profile, i.e., increased levels of both fasting glucose and fasting insulin at baseline ($p < 0.001$). Increased adherence to the Mediterranean diet was inversely associated with the 20-year new T2DM cumulative incidence ($p < 0.001$). Moreover, individuals who did not develop new T2DM had higher adherence to the Mediterranean Diet, both at baseline and follow-up examination ($p < 0.001$). Current smoking was positively associated with the 20-year cumulative incidence of new T2DM ($p < 0.001$). Regarding clinical parameters, higher prevalence of both hypertension and hypercholesterolemia was observed among subjects who developed new T2DM during the 20-years period ($p < 0.001$ in both cases).

As far as lipid profile is concerned, simple markers, i.e., TC, LDL-C, TGs, and non-HDL-C were higher among subjects who developed new T2DM, while HDL-C was lower as compared to those who did not ($p < 0.001$). An additional goal of this study was to evaluate the association between combined lipid markers and T2DM. All combined lipid markers, by the exception of LAP, were higher among subjects who developed new T2DM during the 20-year follow-up as compared to those who did not (Table 2). Regarding family history of T2DM and lipid markers' levels, no differences were observed between those with positive family history of diabetes and the rest of the participants (all p-values > 0.317).

Association between simple and combined lipid markers and 20-year cumulative incidence of T2DM

The previous analyses demonstrated unadjusted associations between lipid profile and T2DM onset. However, residual confounding may exist. Thus, multi-adjusted models were unveiled to evaluate the association between simple and combined lipid markers and the 20-year cumulative incidence of new T2DM, after adjusting for several adjusting variables (Table 3). All simple and combined lipid markers were significantly associated with T2DM cumulative incidence, after adjusting for age, sex, smoking status, physical activity level, MedDietScore, WHR, use of lipid lowering medication, dietary supplements and family history of T2DM. However, when fasting glucose levels were considered, LDL-C/HDL-C and NHHR combined lipid markers remained significantly associated with new T2DM development (p-values < 0.05) (Table 3).

The accuracy of the estimate models was found approximately 0.75 (C-statistic) (Table 3). The net reclassification index (NRI) that evaluated the additive classification value of simple and combined lipid markers to insulin resistance indices, was calculated. It was observed that the inclusion of lipid markers improved the correct classification rate of the models by: 10.6% for the model containing LDL-C ($p < 0.001$), by 8.8% for the model containing TG ($p < 0.001$), by 8.8% for the model containing non-HDL-C, by 8.7% for the model containing TC ($p < 0.001$), by 7.1% for the model containing HDL-C, by 6.9% for the model containing TC/HDL-C ($p < 0.001$), by 6.9% for the model containing NHHR ($p < 0.001$), by 6.5% for the model containing TGs/HDL-C ($p < 0.001$), by 6.5% for the model containing TyG ($p < 0.001$), by 6.1% for the model containing LDL-C/HDL-C ($p < 0.001$) and by 0.9% for the model containing CMI ($p = 0.301$).

Table 1 Baseline sociodemographic, anthropometric, lifestyle, clinical, and biochemical parameters of the ATTICA study participants

	Total sample	New T2DM during 20-year FU	No T2DM during 20-year FU	*p*-value
N	2000	526	1474	
Sociodemographic parameters				
Age; years	42.7 (12.9)	45.2 (12.6)	41.8 (12.9)	< 0.001
Sex				
Female	51.3	21.4	78.6	< 0.001
Male	48.7	78.6	21.4	
Anthropometric parameters				
Body mass index; kg/m^2	25.9 (4.5)	27.0 (4.6)	25.6 (4.3)	< 0.001
Waist circumference; cm	89.1 (15.1)	93.1 (13.9)	87.7 (15.3)	< 0.001
WHR; units	0.85 (0.01)	0.88 (0.01)	0.85 (0.01)	< 0.001
WHtR; units	0.5 (0.08)	0.6 (0.08)	0.5 (0.08)	< 0.001
Lifestyle parameters				
MedDietScore; units (0–55)	26.4 (6.5)	25.8 (6.6)	26.6 (6.4)	0.021
MedDiet trajectories				
Low-low	20.9	27.1	18.6	< 0.001
Low-high	7.9	11.6	6.5	
High-low	48.9	45.5	50.1	
High-high	22.3	15.7	24.8	
Current smoking	25.9	35.4	22.5	< 0.001
Physical activity at baseline	41.8	41.4	41.9	0.87
Clinical parameters				
Hypertension	27.5	35.5	24.7	< 0.001
Hypercholesterolemia	39.2	46.9	36.5	< 0.001
Family history of T2DM	53.4	54.5	53.0	0.901
Biochemical parameters				
Fasting glucose; mg/dL	88.7 (11.1)	104.1 (6.4)	83.7 (8.7)	< 0.001
Fasting insulin; μU/mL	12.5 (2.0)	14.1 (2.9)	11.9 (1.3)	< 0.001
HOMA-IR; units	2.8 (0.7)	3.6 (0.5)	2.5 (0.5)	< 0.001

p-value was based on the Pearson chi-square test (categorical characteristics), on the independent samples t-test (normally distributed continuous variables) and on the Mann-Whitney U-test (not-normally distributed continuous variables); Categorical variables are presented as relative frequencies (%) and continuous variables are presented as mean values [standard deviation (SD)]; Participants' physical activity level was assessed through the short-form International Physical Activity Questionnaire; Subjects who reported smoking ≥ 1 cigarette/day or had ceased smoking within one year were classified as current smokers. *Abbreviations* T2DM: Type 2 diabetes mellitus; FU: Follow-up; SD: Standard deviation; WHR: Waist to hip circumference ratio; WHtR: Waist circumference to height ratio; MedDiet: Mediterranean Diet; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance

Association between simple and combined lipid markers and 20-year cumulative incidence of new T2DM stratified by prediabetes status

To further evaluate the role of insulin resistance in the association between lipid markers and new T2DM development, analyses were stratified by prediabetes status. It was observed that among participants classified at prediabetes status during baseline examination, TC [OR (95%CI) per 1 mg/dL: 1.01 (1.01, 1.02)], HDL-C [OR (95%CI) per 1 mg/dL: 0.98 (0.96, 0.99)], non-HDL-C [OR (95%CI) per 1 mg/dL: 1.01 (1.01, 1.02)], LDL-C [OR (95%CI) per 1 mg/dL: 1.01 (1.01, 1.02)], as well as the combined markers, TC/HDL-C [OR (95%CI) per 1 unit: 1.35 (1.11, 1.63)], LDL-C/HDL-C [OR (95%CI) per 1 unit: 1.36 (1.07, 1.74)], NHHR [OR (95%CI) per 1 unit: 1.35 (1.11, 1.64)], TyG [OR (95%CI) per 1 unit: 2.19 (1.37, 3.51)], were significantly associated with new T2DM onset, after all adjustments made (see for adjusting factors Table 3). Moreover, among normoglycemic participants, TC [OR (95%CI) per 1 mg/dL: 1.01 (0.99, 1.01)] ($p < 0.1$-borderline association), non-HDL-C [OR (95%CI) per 1 mg/dL: 1.01 (1.01, 1.02)], LDL-C [OR (95%CI) per 1 mg/dL: 1.01 (1.01, 1.02)], as well as the combined markers, TC/HDL-C [OR (95%CI) per 1 unit: 1.22 (1.01, 1.48)], NHHR [OR (95%CI) per 1 unit: 1.22 (1.01, 1.48)], TyG [OR (95%CI) per 1 unit: 3.41 (1.75, 6.65)], were significantly associated with new T2DM onset.

Association between simple and combined lipid markers and 20-year cumulative incidence of new T2DM stratified by body weight status

Literature suggest that body weight could play a moderating role concerning the association between lipid markers and onset T2DM. Thus, interaction terms between the lipid markers and waist to hip ratio were introduced in all models presented in Table 3. Some significant interactions were revealed. In particular, the TC/HDL-C

Table 2 Baseline simple and combined lipid markers of the study participants

	Total sample	Developed T2DM during 20-year FU	No T2DM during 20-year FU	*p*-value
N	2000	526	1474	
Simple lipid markers				
Total cholesterol; mg/dL	191.9 (41.1)	202.0 (41.0)	188.6 (40.7)	< 0.001
HDL-cholesterol; mg/dL	48.9 (14.3)	46.3 (11.9)	49.8 (14.9)	< 0.001
LDL-cholesterol; mg/dL	120.7 (37.1)	128.4 (36.6)	118.1 (36.9)	< 0.001
Triglycerides; mg/dL	112.2 (80.2)	130.1 (108.7)	106.6 (67.7)	< 0.001
Non-HDL-cholesterol; mg/dL	142.6 (43.1)	155.2 (42.7)	138.3 (42.4)	< 0.001
Combined lipid markers				
Triglycerides/HDL-cholesterol; units	2.7 (3.0)	3.3 (4.7)	2.5 (2.2)	< 0.001
Total cholesterol/HDL-cholesterol; units	4.2 (1.5)	4.5 (1.6)	4.1 (1.5)	< 0.001
LDL-cholesterol/HDL-cholesterol; units	2.7 (1.2)	2.9 (1.2)	2.6 (1.3)	< 0.001
CMI; units	1.5 (1.8)	1.9 (2.9)	1.3 (1.2)	< 0.001
NHHR; units	3.2 (1.5)	3.7 (1.6)	3.1 (1.5)	< 0.001
TyG; units	8.4 (0.6)	8.7 (0.6)	8.2 (0.5)	< 0.001
TyG*BMI; units	217.8 (45.5)	235.6 (46.5)	212.1 (43.8)	< 0.001
TyG*WHtR; units	4.4 (0.9)	4.8 (0.8)	4.3 (0.9)	< 0.001
LAP; units	41.3 (41.8)	43.0 (42.6)	40.7 (42.5)	0.318

p-value was derived using the independent samples t-test (for normally distributed continuous variables) and on the Mann-Whitney U-test (for not-normally distributed); Continuous variables are presented as mean values [standard deviation (SD)]; Abbreviations: T2DM: Type 2 diabetes mellitus; FU: Follow-up; SD: Standard deviation; LDL-C: Low Density Lipoprotein-Cholesterol; HDL-C: High Density Lipoprotein-Cholesterol; CMI: Cardiometabolic Index; WHtR: Waist circumference to height ratio; NHHR: Non-HDL-cholesterol to HDL-cholesterol ratio; BMI: Body Mass Index; TyG: Triglycerides-glucose index; LAP: Lipid Accumulation Product

ratio was associated with an elevated risk of developing new T2DM by 18% [OR (95%CI) per 1-unit, 1.18, 95%CI (1.02, 1.35)] in overweight/obese subjects, but not associated with new T2DM risk among individuals with normal body weight (p for interaction < 0.001). In addition, an increase in the CMI was associated with 15% elevated risk of developing new T2DM during the 20-year period in overweight/obese subjects [OR (95%CI) per 1-unit, 1.15 (0.99, 1.32)], but not among individuals with normal body weight [OR (95%CI) per 1-unit, 1.28 (0.84, 1.96)] (p for interaction < 0.001). Similarly, an increase of the non-HDL-C to HDL-C ratio was associated with an elevated risk of developing new T2DM by 17% [OR (95%CI) per 1-unit, 1.17 (1.02, 1.35)] in overweight/obese subjects, but not in individuals with normal body weight [OR (95%CI) per 1-unit, 1.22 (0.96, 1.54)] (p for interaction < 0.001).

Discussion

The present study examined the association between a variety of simple and combined lipid markers, and the 20-year cumulative incidence of new T2DM among apparently healthy adults participating in the ATTICA cohort study (2002–2022). Lipid markers were strongly associated with long-term onset of T2DM. However, when glucose levels were considered some of the lipid markers (i.e., TC, and non-HDL-C) lost its significant association, highlighting the complex interplays between lipid profile and glucose metabolism. Additionally, most lipid markers were significantly associated with 20-year T2DM cumulative incidence among prediabetes participants. Moreover, increased body weight seemed to be implicated in the associations of combined lipid markers and T2DM onset, underlying the role of body fat on the association between lipid concentrations and new T2DM. Almost all lipid markers examined, both simple and combined, showed significant additive to insulin resistance, value for the correct reclassification of participants, varied between 0.9% for CMI to 10.6% for LDL-C, who developed T2DM during the 20-year observation period. No significant differences were found between simple and combined lipid markers in relation to their predictive ability of new T2DM or the correct reclassification rate of the participants. Despite the limitations of an observational study, these findings suggest that lipid markers may play a role in more accurately identifying individuals at high risk of developing new T2DM.

T2DM is a metabolic condition in which there is a disrupted feedback loop between insulin secretion and insulin action [26]. Insulin resistance and the dysfunction of the pancreatic β-cells are the main surrogates of T2DM. The implication of lipid abnormalities in the pathogenesis of T2DM has gained much research interest the past few years. According to relatively recent data, insulin resistance has been associated with abnormal lipid profile, and therefore, dyslipidemia is now considered as risk marker for the development of T2DM [27]. Additionally, accumulating evidence suggest that there is a complex interplay between insulin resistance and dyslipidemia, which has been observed both in people with or without T2DM, while the relationship seems to be reciprocal [28]. Abnormalities in lipids levels have shown to influence the risk of developing T2DM [29]. Moreover, in people with established T2DM lipid abnormalities have been associated with even higher risk of coronary artery disease, compared to those with normal lipid levels [30, 31, 33]. Elevated TGs are closely linked to insulin resistance and are a key marker of metabolic dysfunction. High TG levels often indicate poor insulin sensitivity

Table 3 Multi-adjusted logistic regression models evaluating the association between lipid markers, and 20-year cumulative incidence of T2DM

Models *	Unadjusted for fasting glucose		Adj. for fasting glucose		Model accuracy
	OR	95%CI	OR	95%CI	C-statistic*
Model 1: Total cholesterol (per 1 mg/dL)	1.01	1.01, 1.02	0.99	0.97, 1.02	0.749
Model 2: HDL-C (per 1 mg/dL)	0.98	0.97, 0.99	0.92	0.83, 1.01	0.741
Model 3: LDL-C (per 1 mg/dL)	1.01	1.01, 1.02	1.01	0.99, 1.04	0.750
Model 4: Triglycerides (per 1 mg/dL)	1.01	1.01, 1.02	0.99	0.98, 1.01	0.746
Model 5: Non-HDL cholesterol (per 1 mg/dL)	1.01	1.01, 1.02	1.00	0.97, 1.02	0.745
Model 6: Triglycerides/HDL-C (per 1 unit)	1.11	1.02, 1.20	1.11	0.82, 1.51	0.743
Model 7: Total cholesterol/HDL-C (per 1 unit)	1.22	1.08, 1.37	2.09	0.99, 4.67	0.743
Model 8: LDL-C/HDL-C (per 1 unit)	1.17	1.01, 1.36	2.66	1.01, 2.68	0.750
Model 9: CMI (per 1 unit)	1.21	1.06, 1.39	1.25	0.73, 2.17	0.745
Model 10: NHHR (per 1 unit)	1.22	1.08, 1.37	2.10	1.01, 4.67	0.743
Model 11: TyG (per 1 unit)	3.58	2.51, 5.10	1.27	0.23, 7.02	0.750
Model 12: LAP (per 1 unit)	0.99	0.99, 1.01	0.99	0.98, 1.01	0.714

ORs and their corresponding 95%CIs were obtained through logistic regression analysis, as proxy of Relative Risks. *All the above models were adjusted for: age (years), sex (female vs. male), smoking status (yes vs. no), physical activity level (yes/no), MedDietScore, waist to hip ratio, family history of T2DM (yes/no), and dietary supplements related to lipid metabolism. Fasting glucose levels were added in the previous models. **C-statistic is derived from the age-, sex-adjusted models that included the tested simple and combined lipid markers. *Abbreviations* OR: Odds Ratio; CI: Confidence Interval; HDL-C: High Density Lipoprotein – Cholesterol; LDL-C: Low Density Lipoprotein – Cholesterol; CMI: TGs/HDL-C*WHtR: TGs: Triglycerides; WHtR: Waist circumference to height ratio; CMI: Cardiometabolic Index; NHHR: Non-HDL-cholesterol to HDL-cholesterol ratio; TyG: Triglycerides-glucose index; LAP: Lipid Accumulation Product

and are associated with an increased risk of developing T2DM and atherosclerotic cardiovascular disease [32, 33]. Moreover, based on a secondary retrospective analysis on a Chinese cohort study, the TGs/HDL-C ratio was strongly associated with the risk of developing new T2DM, with non-linear relationship [6]. A non-linear relationship was also found in a cohort survey among normoglycemic Japanese men; particularly, a U-shaped relationship between TGs/HDL-C ratio and the risk of developing new T2DM was observed [34]. In our study, after adjusting for various covariates, including fasting glucose, the TGs/HDL-C ratio did not show neither linear nor non-linear relationship with the 20-year cumulative incidence of T2DM.

Higher levels of HDL-C have been associated with improved insulin sensitivity, since HDL can enhance glucose uptake in muscle and fat cells, a process which reduces insulin resistance. According to findings from a study of healthy American adults participated in the National Health and Nutrition Examination Survey, an increment of non-HDL-C/HDL-C ratio by 1 unit increased the risk of developing new T2DM by 8%, with a non-linear association observed, indicating a threshold point at 1.50 [35]. Furthermore, a longitudinal cohort study among Japanese normoglycemic adults reported that non-HDL-C/HDL-C ratio demonstrated a stronger predictable ability concerning the risk of developing T2DM, compared to other conventional lipid indices, i.e., TC, TGs, non-HDL-C, LDL-C, and HDL-C, while specific analysis indicated that the relationship between non-HDL-C/HDL-C ratio and T2DM was non-linear [36]. In the present study, HDL-C levels alone, or implicated in combined markers with TC, LDL-C, non-HDL-C, showed significant associations with T2DM onset, irrespective of participants' insulin resistance status, as well as lifestyle-related habits strongly associated with diabetes. Although, HDL-C levels along or implicated in combined lipid markers, was significantly associated with T2DM onset, in overweight/obese individuals, with no similar association in subjects with normal body weight, indicating the possible implication of excess body fat in the relationship between T2DM onset and lipid markers.

Concerning TyG index, a surrogate of insulin resistance, several cohort studies among normal-weight nondiabetic participants indicated a positive association between TyG and the cumulative incidence of new T2DM [19, 37]. The PURE study also demonstrated that TyG, was positively associated with increased cardiovascular mortality and T2DM cumulative incidence as well, underlying the pivotal role of insulin resistance, concerning the pathogenesis of several metabolic diseases [38]. In line with previous studies, in our study the TyG index demonstrated a strong ability in predicting T2DM during the 20-year period, in both prediabetes and normoglycemic participants, as well as in both normal and overweight/obese individuals. However, it should be noted that when fasting glucose levels were considered TyG was not significantly associated with new T2DM onset, suggesting that glucose levels distribution deserves further investigation in the study between TyG index and diabetes.

Obesity is a multifactorial, relapsing, chronic disease, which is considered a proxy of a plethora of several metabolic diseases, including T2DM. Obesity plays a synergistic, moderating role in the relationships of several predisposing factors and new T2DM [39]. According to

findings from a cohort study among middle-aged and elderly Chinese, obesity related markers, in terms of body mass index, waist circumference, and waist-to-height ratio, demonstrated a modest predictable ability, concerning T2DM cumulative incidence. Similarly, recent data from the China Health and Retirement Longitudinal Study concluded that the TyG index had the greatest predictable ability for new T2DM in both male and females, while its combination with waist circumference, body mass index, and waist-to-height ratio, outperformed obesity related indices, i.e., waist circumference, body mass index, and waist-to-height ratio, in forecasting new T2DM. Worth noting, the TyG index outperformed other obesity related markers, in predicting new T2DM, among normal weight Chinese elder subjects, suggesting the possible moderating role of obesity and/or overweight, regarding the above association [40].

In the present study, significant interactions between lipid markers and obesity status were revealed. In particular, the TC/HDL-C ratio, or non-HDL-C to HDL-C ratio, was associated with an elevated risk of developing T2DM only in overweight/obese subjects. Similarly, CMI was associated with elevated risk of developing T2DM during the 20-year period only among overweight/obese. It seems that obesity amplifies the adverse effects of lipid abnormalities, making these markers more closely associated with the development of new T2DM. These findings underline the need for risk stratification by obesity status when evaluating lipid markers for future T2DM development.

T2DM has been strongly associated with the family history, indicating the major role of genetics in the development of the disease. However, whether family history of T2DM affects individuals' lipid profile levels is not well studied and understood. In the present study, no associations were found regarding lipids profile of the participants and family history of T2DM; however, this cannot be considered as a lack of an association or a mechanism, as the sample of participants with family history was relatively small, and inadequate to establish robust associations or lack of accusations.

Mediterranean diet is of great importance, concerning the secondary prevention of T2DM. According to recently presented data from the ATTICA Study, the long-term adherence to the Mediterranean diet played a protective role, regarding the development of T2DM, during the 20-year period of follow-up. Specifically, individuals consistently close to the Mediterranean diet throughout the studied period had an improved glycemic and lipidemic profile and showed a 21% reduction in their 20-year risk of developing T2DM compared to those who were consistently away. Thus, a long-term adherence to the Mediterranean diet is protective against the onset of T2DM and, therefore, could be incorporated in public health actions for the prevention of the disease [41]. In the present analyses, adherence to the Mediterranean diet did not influence the associations between simple or combined lipid markers and cumulative incidence of T2DM, when MedDietScore was used as an adjusting covariate in the models.

Strengths and limitations

The ATTICA study is a large-scale prospective observational survey with a large period of follow-up, i.e., 20 years, that makes the present study one of the few in the epidemiology of diabetes, worldwide. However, the results should be interpreted cautiously, because the effect of residual confounding may still exist due to the observational design of the study. Use of statins is a common treatment for elevated lipid levels; although this factor was considered in the analyses, the exact dose, and duration of statin use was not accounted for, and therefore may bias the results. The exact date of the development of new T2DM was not available, making the calculation of T2DM incidence rate unfeasible. The lipid markers assessment was conducted only at baseline examination. Moreover, the classification of body weight status, according to BMI, has significant limitations in assessing obesity, particularly among individuals with moderate or high-intensity physical activity. In addition, body composition analyzers were not used, and screening individuals regarding muscle mass was not performed; therefore, participants with high muscle mass who were classified as overweight may exist in the sample. Dietary assessment was performed through validated semi-quantitative questionnaires, a procedure which may involve recall bias due to misreporting or/and underreporting of dietary and lifestyle habits. Except for recall bias, selection bias due to 25% loss to follow-up, and classification bias (i.e., misdiagnosis of diabetes), are also considered among the limitations of the present study.

Conclusions

This cohort study showed that lipid profiles are linked to the long-term development of T2DM. Whether evaluated through simple or combined markers, lipid profile may aid in identifying and improving risk stratification for individuals at high risk of T2DM, as well as enhancing the effectiveness of primary prevention management and public-health strategies.

Abbreviations

T2DM	Type 2 diabetes mellitus
DALYs	Disability-adjusted life years
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TGs	Triglycerides
LAP	Lipid accumulation product
WC	Waist circumference

WHR	Waist circumference to hip ratio
BMI	Body mass index
CMI	Cardiometabolic index
NHHR	Non-high-density lipoprotein cholesterol/high-density lipoprotein cholesterol
TyG	Triglycerides-glucose index
MedDiet	Mediterranean diet
MedDietScore	Mediterranean score
IPAQ	International physical activity questionnaire
SD	Standard deviation
ANOVA	One-way analysis of variance
RR	Relative risk
CI	Confidence interval
NRI	Net reclassification index
FU	Follow up
WHtR	Waist circumference to height ratio
OR	Odds ratio
SIDIAP	System for the Development of Research in Primary Care

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Author contributions
Conception, drafting the paper, I.K.; acquisition, analysis, interpretation of data, creation of new software used in the work, revision, design, C.C., C.P., C.T., E.L., P.P.S. and D.P. All authors have read and approved the submitted version of the manuscript, and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Institutional review board statement
The ATTICA study was conducted in accordance with the Declaration of Helsinki (1989) of the World Medical Association and was approved by the Institutional Ethics Committee of Athens Medical School (#017/1.5.2001). All participants were informed about the aims and procedures and agreed to participate providing signed written consent.

Consent for publication
Consent for publication is available on request from the corresponding author.

Informed consent
Informed consent was obtained from all subjects involved in the study.

Competing interests
The authors declare no competing interests.

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